Review paper

An update on the coronary calcium score: a review for clinicians

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Adv Interv Cardiol 2022; 18, 3 (69): 201–205
DOI: https://doi.org/10.5114/aic.2022.121035

Abstract

The clinical manifestation of coronary artery atherosclerosis is coronary artery disease (CAD) with symptoms ranging from exertional chest pain due to reduction of coronary flow reserve to acute coronary syndrome due to rupture of usually a nonobstructive plaque with abrupt coronary blood flow reduction. CAD is the leading cause of morbidity and mortality worldwide. Therefore, identifying asymptomatic people at risk of CAD is pivotal to guide decision-making for primary prevention. Coronary artery calcium (CAC) is a hallmark of coronary artery atherosclerosis. It can be detected using cardiac computed tomography and quantified by the Agatston method. CAC examination is a cheap, fast and low radiation dose test, without injecting a contrast agent. It provides prognostic information over other traditional cardiovascular risk markers and established scoring systems, especially for low-risk subgroups such as women and younger adults, and indicates the appropriate moment to implement primary prevention, including acetylsalicylic acid and statins. In this review, we discuss the methods of CAC evaluation, the meaning of a zero CAC score (CACS), its conversion to CACS > 0 and the impact of this fact on cardiovascular risk, the effect of statins and proprotein convertase subtilisin/kexin type 9 inhibitor on CAC progression, interpretation of CACS results, and CACS prognostic value in both asymptomatic and symptomatic patients.

Key words: computed tomography, coronary artery calcium, coronary artery disease.

Introduction

Coronary artery disease (CAD) is a symptomatic phase of coronary atherosclerosis and is the leading cause of morbidity and mortality worldwide. It is responsible for over 70% of sudden cardiac deaths [1]. The clinical manifestation of coronary atherosclerosis usually appears after the fourth decade of life or later, but is preceded by the presence of coronary artery calcifications (CAC), highly specific for atherosclerosis. Detection of any calcification in the walls of the coronary arteries on computed tomography (CT) means atherosclerosis and provides prognostic information over other traditional cardiovascular risk markers and established scoring systems, especially for low-risk subgroups [2, 3].

In this review, we discuss methods of CAC evaluation, the meaning of a zero CAC score (CACS), its conversion to CACS > 0, the effect of statins and proprotein convertase subtilisin/kexin type 9 inhibitor on CAC progression, interpretation of CACS results, and CACS prognostic value in both asymptomatic and symptomatic patients.

Methods of CAC evaluation

Coronary artery calcium can be detected using electron beam computed tomography (EBCT) and more recently multi-slice CT. The scanning and processing time is extremely fast (approximately 15 min), the effective radiation dose is low (approximately 1 mSv) and no contrast agent is needed. CAC can be estimated semi-quantitatively using three methods: the mass equivalent score, the volume score and the most widely used Agatston score. All these scoring methods are strongly correlated with each other [4]. The CAC value by the Agatston method is calculated by multiplying the area of calcified plaque by the density score. The density score for 130–199 Hounsfield units (HU) is equal to 1; for 200–299 HU is 2; for 300–399 HU is 3; and a density score of 4 corresponds to 400 HU. For example, if a calcified speck oc-

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Received: 7.09.2022, **accepted:** 11.10.2022.

cupies an area of 6 mm² and the maximum attenuation is 400 HU, the score will be 24 AU. Absence of calcium is considered as a "negative" examination or zero CAC score (CACS). In the presence of CAC, the score of each calcified plaque is summed to give the total CACS.

Zero CACS

CAC evaluation alone might not allow the assessment of the early stage of plaque formation ("low attenuation plaques"); however, zero CACS practically excludes coronary atherosclerosis in subjects with a low pre-test probability of CAD [5]. In one current pooled analysis, the incidence of obstructive CAD (defined as luminal stenosis of ≥ 50%) using CT coronary angiography in symptomatic patients without CAC was 4.4% [6].

The prevalence of low cardiovascular risk in subjects with zero CACS has been demonstrated in large registries and clinical trials [7–11]. In a multicentre trial of 19,898 asymptomatic patients with zero CACS, the 10-year all-cause mortality rate was less than 1% [7]. In another multicentre, retrospective cohort study of 29,757 asymptomatic participants without CAC, followed for 12 years, rates of deaths from coronary heart disease (CHD) and cardiovascular disease (CVD) ranged from 0.32 to 0.43 per 1,000 person years [8].

Similar observations were found in symptomatic subjects, e.g. in the multicentre international Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry during a mean follow-up of 2.1 years, the mortality rate of symptomatic patients with zero CACS was 0.4% [9]. Similar findings were found in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial [10]. In another observational cohort sample of 1,978 patients with zero CACS and stable chest pain or dyspnoea with a mean follow-up of 5.2 ± 2.8 years, there were no deaths due to CHD. Moreover, the negative predictive value for severe stenosis was 99.5% [11].

Therefore, due to the very low risk of CHD events, patients aged 45–84 with zero CACS should be rescanned no earlier than 3 to 5 years, depending on individual demographics and risk profile [12]. According to Lehmann *et al.,* in subjects (mean age: 58.7 ±7.5) with zero CACS at baseline and no conversion to positive CACS through 5 years of follow-up, no further CT scan is required [13].

Overall, zero CACS is associated with a low risk of death in both asymptomatic and symptomatic patients, and according to the American College of Cardiology Foundation guidelines, patients with zero CACS do not need to take statins to reduce their elevated cholesterol level unless they are cigarette smokers, have diabetes mellitus or have a family history of premature CAD [14]. In our opinion, this list should be completed with prominent thoracic aortic calcium (TAC), for which primary prevention with statins to treat hypercholesterolemia is also reasonable. However, in the MESA study (Multi-Ethnic Study of Atherosclerosis) TAC did not improve 10-year estimation of prognosis beyond traditional risk factors [15]. According to the MESA data, in subjects without diabetes, the net harm from aspirin use occurred when CACS was zero and a net benefit was seen when CACS was ≥ 100 AU [16].

From zero to positive CACS (CACS > 0)

The likelihood of developing CAC increases non-linearly with age [17]. The MESA study demonstrated that the incidence of newly detectable CAC was on average 6.6% per year and increased with age, ranging from < 5% per year in those aged < 50 years to > 12% in those aged > 80 years [18]. If CAC occurs early during the lifespan, it has more clinical implications than in the elderly. For example, among individuals aged between 32 and 46 years, CACS of 100 AU or more is associated with premature death [19]. In young symptomatic individuals, even a minimal CACS (1–10 AU) significantly increased the CHD event rate [19, 20]. Lehmann *et al.* identified potential cardiovascular risk factors related to conversion from zero CACS to positive CACS, such as age, high systolic blood pressure, elevated LDL cholesterol and current smoking [21]. An interesting study by Brodov *et al.* showed that the odds of CAC conversion were higher in patients with higher levels of TAC. Moreover, in multivariate analysis, a TAC score of ≥ 100 AU was an independent predictor of zero CACS conversion [22]. Based on the results of the genetic risk score, it seems that it might be possible to estimate the best time to perform the first CT scan to predict the conversion time [23]. The moment of CACS conversion from 0 to positive is critical, because from then on CACS only progresses exponentially. When CACS is 100 AU or more, it is high time to initiate preventive treatment including acetylsalicylic acid and statins [2, 16, 17]. In terms of primary prevention, selective use of screening for CAC might be considered in relatively young individuals with abundant coronary risk factors or genetic traits of atherosclerosis.

Does CACS progression mean plaque progression or plaque stabilization?

As already mentioned, CAC progresses exponentially during consecutive decades of life [17, 19]. It is considered that more rapid progression of CACS is associated with worse clinical outcomes [24]; however, a large prospective and observational study in subjects aged 45 to 74 years showed that none of the ten different CAC progression algorithms were superior at predicting CHD and CVD events based on risk factors, baseline CACS, or CACS after 5 years of follow-up [13]. There are no known pharmacological methods leading to CAC regression, and even use of statins is associated with the progression

of calcifications [25–27]. Indeed, a meta-analysis of five controlled trials showed continuing progression of coronary calcification despite statin treatment [28]. Despite the acceleration of CACS progression during treatment with statins, statins decrease the percent atheroma volume and reduce the risk of major adverse cardiovascular events [25]. This calcium paradox is most likely related to changes in plaque features (increasing plaque calcium content) and causes plaque stabilization. One study found that annual progression of CACS could be slowed by adding a proprotein convertase subtilisin/kexin type 9 inhibitor to statin therapy [29].

Annual CACS progression typically ranges from 20% to 25%, but the rate of progression depends on risk factors, especially diabetes [18, 30].

Nevertheless, given the current CACS and age, it is possible to estimate the age at which the CACS was converted from zero to positive [31], which is related to the concept of arterial "age" and will be discussed in the next section.

Interpretation of CACS results

CACS correlated with atherosclerotic plaque burden, but not with luminal area stenosis. The CACS result can be graded on a scale from 0 to over 400 AU. According to the Mayo Clinic guidelines, in patients with extensive CACS (> 400 AU), the likelihood of significant coronary artery stenosis is more than 90%, especially in patients with a higher pre-test probability [32]. This risk stratification was originally extensively validated based on EBCT acquisitions.

Another useful CAC scale involves calculation of arterial "age". Such a calculator can be found on the MESA website (http://www.mesa-nhlbi.org/Calcium/ArterialAge.aspx). The "age" of the subject's arteries is the adjustment of age to his CACS. This conversion from the AU to the age scale is more understandable to patients (e.g. you are 55 years old, but your arteries are more diseased and correspond to those aged 65 years). The close relationship between CAC and age, and the underestimation of the CVD risk in young individuals and women, mandates an assessment according to age and gender. Raggi *et al.* demonstrated that CACS percentiles based on patient age and gender are better predictors of CHD events than CACS or risk factors in an asymptomatic population. According to their assumptions, treating patients above the 75th percentile would avoid approximately 70% of hard CHD events [33].

A similar percentile nomogram was based on the MESA study, and it is available on the MESA website (http://www.mesa-nhlbi.org/Calcium/input.aspx). The larger percentile scale from a pooled analysis including a greater number of women, residents of countries outside the USA, young individuals and the elderly was created by de Ronde *et al.* [34]. Such a percentile calculator can be found on the Amsterdam University Medical Center website (https://www.calciumscorecalculator.com). According to the American guidelines for primary prevention, in individuals with an intermediate CVD risk a CACS equal to or higher than 100 AU or the 75th percentile from the MESA nomogram reclassifies risk upward; therefore statin therapy should be initiated [2]. According to the European guidelines on cardiovascular disease prevention in clinical practice, the observed CACS should be compared with the expected CACS depending on the patient's age and sex. A higher than expected CAC increases the individual's calculated risk, whereas the performance of the CAC examination should depend on local and regional availability and cost-effectiveness, and is especially useful for those with an intermediate CVD risk [35].

Prognostic value of CAC in asymptomatic patients

Assessment of CAC has emerged as the most predictive single cardiovascular risk marker in asymptomatic patients, both men and women, younger (< 40 years) and older (> 65 years) [36]. CAC is capable of reclassifying patients with an intermediate risk for CAD [2]. Silverman *et al.* assessed the relationship between CAC distribution and the need for revascularization. They demonstrated that the greater the plaque burden or the number of diseased vessels, the greater the likelihood of revascularization. Even after adjustment for CACS, the number of diseased vessels remained a significant predictor of revascularization and mode of revascularization (percutaneous coronary intervention or coronary artery bypass graft) [37]. In a prospective multi-ethnic cohort trial of 6,814 asymptomatic subjects aged 45–84 years over a median of 11.1 years, a positive association was found between CAC strata and the risk of a future CVD event, regardless of age, gender, or race/ethnicity [38]. These large observational studies demonstrated that CAC presence in asymptomatic individuals is associated with an increased risk of future CVD.

10-year CHD risk assessment for CACS was based on the MESA study (website calculator available on: https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx).

Prognostic value of CAC in symptomatic patients

A large meta-analysis that evaluated 34,041 stable, symptomatic patients from 19 observational studies revealed a positive association between CACS and major adverse cardiac events [39]. Mortensen *et al.* followed 23,759 symptomatic subjects for 4.3 years, and the incidence of CVD events increased with higher CACS [40]. Another study of 3,691 symptomatic young subjects (18–45 years of age) with a median follow-up of 4.1 years showed that the highest event rate occurred in

Table I. Take-home messages

- Zero CACS means a very good prognosis, at least in the next few years.
- The moment of CACS conversion (onset of coronary atherosclerosis) is difficult to capture, but important in terms of prognosis and treatment.
- Statins accelerate the annual progression of CACS, which is explained by the stabilization of atherosclerotic plaques.
- Interpretation of CACS results should be related to the "arterial age."
- CACS frequently allows reclassification of cardiovascular risk and provides more tailored prognostic information in asymptomatic and symptomatic patients.

CACS – coronary artery calcification score.

patients with more than 3 risk factors and CACS > 10 AU compared to CAC = 1–10 and CAC = 0 regardless of the number of risk factors [20]. To sum up, CAC scanning in symptomatic subjects provides incremental prognostic information to guide the choice of diagnostic and therapeutic options.

Summary

CAC is a marker of atherosclerosis that can be quantified with cardiac CT. CAC scoring has become a widely available tool for cardiovascular risk classification. Zero CACS is associated with a low risk of cardiovascular events and may serve as a gatekeeper for additional diagnostic tests. The moment of CACS conversion is crucial for prognosis and initiation of statin therapy, yet difficult to capture. CAC progression is higher in statin-treated patients, but this calcium paradox may be related to plaque stabilization. CAC scans are generally scored using the Agatston score; however, age- and gender-based CAC percentiles seem to be better than the CACS alone to define patient risk. A more understandable form for the patient may be to present CACS as arterial "age". We currently have sufficient scientific evidence to use the CACS in both asymptomatic and symptomatic patients to predict cardiovascular risk. Take-home messages are shown in Table I.

Acknowledgments

This work was supported by the National Science Centre (Poland) (grant number: UMO-2017/27/B/ST8/01046).

Conflict of interest

The authors declare no conflict of interest.

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